REMARKS

This Amendment is being filed in response to the Office Action dated October 26, 2009.

Claims 77 and 94 have been amended to more specifically define the solvent employed in step (i) and the suspension formed in step (iii) of the presently claimed method. Specifically, in both claims 77 and 94 the solvent in step (i) has been defined as "non-aqueous" and the suspension formed in step (iii) has been defined as "aqueous". Additionally, the solvent removed during step (iv) has been defined as the "non-aqueous" solvent, which is removed from the "aqueous" suspension. Support for these amendments can be found on page 3, final paragraph to page 4, first paragraph of the application as filed, which describes suitable solvents for use in the invention. The solvents have "high solvent volatility (boiling point lower than that of water), and no, or few, water azeotropes" and are preferably anhydrous. *Id.* The solvent is intended to be easily separable from water, and an aqueous solvent would therefore by unfit for the intended purpose. The addition of water at step (iii) inherently results in the formation of an aqueous suspension, which is then maintained throughout all subsequent steps. Further support for these amendments can be found throughout the application as filed (*see* Examples 1-3 at pages 9-11, wherein non-aqueous solvents such as alcohol are used to form the solution of drug and solvent).

On pages 5-6 of the Office Action the Examiner rejected claims 77-80 and 82-98 under 35 U.S.C. §112, second paragraph.

Reconsideration is requested.

Claims 77-80 and 82-98 are alleged to be indefinite "because it is unclear how the steroid [of step v] is still in suspension if the all [sic] of the solvent is removed." *See* Office Action at page 5, last paragraph. As described above, Claims 77 and 94 have been amended to specify that the solvent is non-aqueous, and the suspension formed by the addition of water is an aqueous suspension. It is respectfully submitted that based upon the present amendments a skilled artisan would understand the terms "non aqueous solvent" and "water" as used in the pending claims are mutually exclusive terms.

In the present invention water is added to a solution of steroid and non-aqueous solvent, forming an aqueous suspension comprising water, a steroid and a non-aqueous solvent. Optionally, the non-aqueous solvent is then removed, in whole or in part, leaving steroid suspended in water. The non-aqueous solvent thus may be removed. An aqueous suspension of steroid remains.

Based on the above amendments and remarks, Applicants respectfully request the 35 U.S.C. §112, second paragraph rejection be withdrawn.

On pages 6-12 of the Office Action, the Examiner rejected claims 77-80 and 82-98 under 35 U.S.C. §103(a) as being unpatentable over United States Patent No. 6,187,765 (hereinafter "Harris").

Reconsideration is requested.

The present invention recites a method for forming a sterile pharmaceutical composition comprising dissolving a steroid in a non-aqueous solvent to form a sterile solution, combining the sterile solution with water to form an aqueous suspension followed by removal of all or part of the non-aqueous solvent from the aqueous suspension. The aqueous suspension is then treated to yield a desired mass median diameter, combined with a pharmaceutically acceptable carrier and stored in sterile containers. Claims 94-98 recite the same method but are limited to a method for forming sterile pharmaceutical compositions comprising budesonide.

As acknowledged by the Examiner, Harris does not teach a method wherein the steroid stays in suspension after the solvent is removed (*see* October 26, 2009 Office Action at page 8, first full paragraph). However, the Examiner alleges that the additional steps of removing the solvent by filtration and drying as taught by Harris are not excluded by Applicants' claim language. Furthermore, the Examiner alleges that these steps are not essential as there is no material effect on the end product. Applicants respectfully disagree.

The method recited in amended claims 77 and 94 does not include any drying step as taught by Harris. Each step of the method utilizes the solution or suspension obtained in a preceding step. Further, the step of removing the non-aqueous solvent (step iv) occurs only after water has been added to form an aqueous suspension with the steroid. Thus, even if all of the non-aqueous solvent is removed in step (iv), the steroid remains in an aqueous suspension.

Therefore, Applicants' method does not, and cannot, comprise an intermediate drying step because such a step would be in conflict with a method which yields an aqueous suspension of a pharmaceutical composition as required by claims 77 and 94.

The Examiner contends on page 7 of the Office Action that Example 1 of Harris teaches a method of preparing a sterile suspension of a steroid, namely, mometasone furoate. Applicants respectfully disagree. Example 1 of Harris produces sterile mometasone furoate monohydrate by a process that finishes with a drying step to produce a ***dry*** product (step 10 of Example 1, Col. 6, lines 58-62). This dry product is then used to formulate various

pharmaceutical compositions, each having different concentrations of active and excipients (*see* Harris at Examples 2, 3, 5 and 6). Therefore Example 1 of Harris only teaches the production of a dry mometasone furoate product, in contrast to a steroid in a suspension combined with a pharmaceutically acceptable carrier and stored in sterile containers as required by the pending claims.

Furthermore, it would not be obvious for the skilled artisan to combine the processes of Examples 1 and 2 of Harris, as noted on page 8 of the Office Action, to arrive at the present invention simply by omitting the drying step of Example 1. The suspension of Example 1 (last present in step 8) comprises sterile mometasone furoate monohydrate in suspension with water and acetone. Example 2 begins by preparing a sterile excipient solution of polysorbate 80, citric acid monohydrate, sodium citrate dihydrate and sodium chloride, to which a precise number of grams of dry mometasone furoate monohydrate are added. Thus, if the mometasone furoate monohydrate were still in suspension, there would be a number of problems including: (i) the presence of acetone in the suspension, whereas this would previously have been removed by drying; and (ii) the mometasone furoate monohydrate would be in a dilute suspension comprising a large amount of water, making it difficult to calculate the precise amount of mometasone furoate monohydrate present. This dilute suspension could not simply be added to the excipients prepared in steps 1 and 2 of Example 2 without a significant number of calculations and alterations to the process of Example 2.

Additionally, if Example 2 is directly followed as taught in Harris, the dry pharmaceutical component is only dissolved in an aqueous solution. There is no use of a non-aqueous solvent in Example 2, and therefore no step in which a non-aqueous solvent is removed from an aqueous suspension comprising the pharmaceutical component and water as required by claims 77 and 94 of the present application.

Therefore, to convert the two stage method of Harris into the single stage method of Applicants' invention would require the skilled artisan to make a significant number of complex changes to the processes of Example 1 ***and*** Example 2.

The skilled artisan reading Harris would understand that the two stage method is essential and moreover, even if they were seeking a simpler method it would not be obvious to make significant amendments to both parts of the Harris method in order to combine the separate processes. It would be far easier to follow the Harris method exactly as set out, producing dry sterile mometasone furoate monohydrate and mixing this with excipients as desired.

Additionally, Harris teaches that "[i]t is preferred to produce the mometasone furoate monohydrate under sterile conditions, conduct the drug micronization in a sterile environment, and perform a sterile packaging operation" *see* Harris at Col. 5, lines 52-55. This statement, read in combination with examples 1, 2, 3, 5 and 6, provides additional direction to the skilled artisan that the processes of Harris are separate and distinct parts of an at least two stage method.

The essential first stage of the method of Harris is to produce ***dry*** sterile mometasone furoate monohydrate. The second stage of Harris involves introducing the dry sterile mometasone furoate monohydrate into formulations containing suspensions. Conversely, Applicants' claimed invention provides a single stage method for preparing a sterile pharmaceutical composition comprising a steroid in suspension. *In re Freed*, 425 F.2d 785 (CCPA 1970) discusses the situation where the claimed invention was a single stage process for producing calcium pantothenate, whereas the prior art disclosed a two stage reaction. The court held that the single stage process was not obvious over the two stage process disclosed in the prior art. The court explained that

> .....it seems more logical and reasonable to infer that one teaching a chemical reaction process would set out the least number of reactions thought necessary to accomplish the desired objective.

Id. at 788.

Thus, following the clear teaching of Harris that a two stage method is essential to yield a formulation containing a drug in suspension, a single stage method would not be obvious to the skilled artisan.

In summary, the method of the present invention does not merely amount to a combination of Examples 1 and 2 of Harris with the removal of the drying step in Example 1. Rather, the method of the present invention employs a single stage method for producing pharmaceutical compositions comprising aqueous suspensions of steroids that is not obvious from the teachings of Harris.

Based upon the foregoing amendments and representations, Applicants respectfully submit the rejections of the claims in the above-identified application have been overcome and should be withdrawn. Early and favorable action is earnestly solicited. If the Examiner does not believe the pending claims are in the form for allowance, Applicants invite the Examiner to call the undersigned to discuss ways to further expedite prosecution of this application.

An early and favorable action is earnestly solicited.

Respectfully submitted,

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